EFFECTS OF THREE ANTIARRHYTHMIC DRUGS ON ACTION POTENTIAL CHARACTERISTICS AND KINETICS OF USE-DEPENDENT BLOCK OF CANINE PURKINJE FIBERS

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The effects of flecainide (FLEC); encainide (ENC); ethmozin (ETHM); and an encainide metabolite (ODE) on transmembrane action potentials (AP) and kinetics of use-dependent block were studied in adult canine Purkinje fibers using standard microelectrode techniques. At BCL=1.5 sec, only ENC 10^{-5}M decreased maximum diastolic potential (MDP) (-90±0.8 to -80±0.3 mV ±SE p<.05). AP amplitude was reduced (p<.05) at 10^{-5}M by FLEC (123±1 to 114±2 mV); ENC (127±3 to 112±1 mV); ETHM (124±1 to 104±9 mV) and at 10^{-6}M by ODE (125±1 to 116±2 mV). $\dot{V}_{max}$ was reduced (p<.05) at 10^{-5} M by FLEC (713±17 to 450±14 V/sec); ENC (676±26 to 427±18 V/sec); ETHM (673±16 to 283±17 V/sec) and at 10^{-6} by ODE (704±16 to 489±18 V/sec). AP duration to 50% repolarization was reduced (p<.05) at 10^{-5} by FLEC (250±17 to 97±11 msec) and ENC (263±17 to 111±9 msec) and at 10^{-6} M by ETHM (275±11 to 193±10 msec) and ODE (277±13 to 152±10). Time constants of onset (τ_{on}) and recovery (τ_{off}) from use-dependent block were estimated from changes in $\dot{V}_{max}$ during and after pacing at BCL=.5 sec. At 10^{-5} M τ_{on} for ETHM (8.2±0.4 beats) was less than (p<.05) FLEC (12.2±0.6) and ENC (10.8±0.5). ODE 10^{-5} M rendered all PF at BCL 0.5 sec inexcitable. At 10^{-5} M ETHM had a shorter τ_{off} than FLEC and ENC (13±0.4 vs. 24±2 and 26±3 sec respectively). We conclude that ENC, ODE and FLEC have more potent use-dependent effects than ETHM, which may be predictive of differing effects of these drugs on conduction in situ.

TRANSCAINIDE: BIOCHEMICAL EVIDENCE FOR STATE-DEPENDENT INTERACTION WITH THE CLASS I ANTIARRHYTHMIC DRUG RECEPTOR

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Transcainide (T) is a new very potent lidocaine analogue with nearly irreversible recovery kinetics. Contradictory electro-physiologic data suggest that T may or may not show state-dependent binding to the class I drug receptor. This study has biochemically assessed if binding of T to its receptor is state-dependent. The radioligand was [^{3}H]batrachotoxinin ([^{3}H]BTXB) which binds to activated sodium channels (SC). Drugs which ↑ the rate of dissociation (k_{-1}) of [^{3}H]BTXB must bind to SC to which [^{3}H]BTXB is already bound (i.e. activated). Drugs which allosterically ↓ the rate of association (k_{+1}) of [^{3}H]BTXB must bind to SC to which [^{3}H]BTXB is not already bound (i.e. nonactivated). T inhibited equilibrium [^{3}H]BTXB binding, IC_{50}=0.5μM. T ↑ k_{-1} of [^{3}H]BTXB but at a concentration much higher than its IC_{50} for inhibition of equilibrium [^{3}H]BTXB binding, EC_{50}=400μM. T also ↓ k_{+1} of [^{3}H]BTXB but at a much lover concentration, EC_{50}=0.25μM. The markedly different k_{-1} and k_{+1} EC_{50} values indicates that the interaction of transcainide with its receptor is state-dependent.

VOLTAGE-DEPENDENT MODIFICATIONS OF Vmax RECOVERY FROM USE-DEPENDENT BLOCK BY CLASS I DRUGS IN GUINEA-PIG PAPILLARY MUSCLES.

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It may be of importance to examine electrophysiological effects of Class I drugs on depolarized myocardium because these drugs are often used for arrhythmias originating from diseased myocardium with resting membrane depolarization. In the present study recovery kinetics from use-dependent block of Vmax (the maximum rate of rise of action potentials) by six Class I drugs, i.e., quinidine (Q, 20uM), mexiletine (M, 30uM), flecainide (F, 5uM), disopyramide (D, 20uM), penticainide (Pe, 50uM) and pirmenol (Pi, 10uM), were evaluated in normally-polarized papillary muscles in 4mM $[K^+]o$ and partially-depolarized preparations in 8mM $[K^+]o$. Use-dependent block at 2Hz by any of these drugs was potentiated by depolarization of resting membrane potential with high K^+ solution. However, the recovery time constants from use-dependent block for D, Pe and Pi were shortened whereas those for Q, M and F were prolonged by depolarization of resting membrane potential (Table). Thus, D and its analogue including Pi and Pe show a potential-dependency of recovery kinetics different from other Class Ia (Q), Ib (M) and Ic (F) drugs.

	Q	M	F	D	Pe	Pi
4 mM K^+	7.6	0.7	18.9	136.7	62.8	24.3 s
8 mM K^+	9.2	1.8	25.1	23.5	33.5	18.6 s

Tuesday, March 20, 1990
4:00PM–5:30PM, Room 6
Cardiac Transplantation: Allograft Arteriopathy

SMALL VESSEL CORONARY ARTERY DISEASE IN CARDIAC TRANSPLANT PATIENTS

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Pathologic studies have demonstrated small vessel arteriosclerosis in the coronary arteries of transplanted hearts, a process triggered by immune-mediated damage to the endothelium. The effects of this disease on resistance vessel function are unknown. To investigate small vessel function in patients with transplanted hearts, coronary blood flow (CBF) responses to the endothelium-dependent dilator acetylcholine (Ach) (10^{-8} to 10^{-6}M) and the smooth muscle dilator adenosine (10^{-6} to 10^{-4}M) were assessed in 40 studies of 29 transplant patients (TX) one to three years after transplantation and 7 nontransplanted controls. CBF was measured in the left anterior descending coronary artery with a Doppler catheter. Controls, year 1 TX, and year 2 TX had similar increases in CBF to Ach (232±40%, 206±40%, 204±53% respectively, p=NS) whereas year 3 TX only increased CBF 106±38%, p<0.05 vs controls). Maximal responses to adenosine did not differ significantly among controls and groups of transplant patients. An index of the proportion of coronary flow reserve attributable to endothelium-dependent dilation was obtained by normalizing each patient's peak acetycholine flow response by his/her peak adenosine flow response. In the patients receiving both acetycholine and adenosine, controls and year 1 TX had similar endothelium-dependent flow responses (56±9% and 56±10%, respectively) but the response seemed to decline in year 2 TX (46±11%) and was significantly diminished in year 3 TX (29±9%, p<0.05 vs controls). By multivariate linear regression analysis, only an increased mean cyclosporine level (range 96 to 292 ng/ml) was an independent predictor of a preserved microvascular response to acetylcholine (B=1.3, p=0.004). Recipient and donor age, sex, pretransplant history of ischemic heart disease, active rejection on biopsy, mean cholesterol level and total episodes of rejection were not predictive. Thus, transplanted hearts develop progressive loss of microvascular endothelium-dependent dilation which may reflect underlying graft arteriosclerosis and contribute to ischemic damage of the myocardium. Higher cyclosporine levels may protect the coronary microvascular endothelium from immune-mediated damage.